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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Docket No: Q67507
Keiichi KAWAI, et al.	
Appln. No.: 10/018,745	Group Art Unit: 1616
Confirmation No.: 2602	Examiner: Dameron L. JONES
Filed: December 21, 2001	

For: METHOD OF THE ADMINISTRATION OF DRUGS WITH BINDING AFFINITY FOR PLASMA PROTEIN AND PREPARATION TO BE USED IN THE METHOD

APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 1.192, Appellants submit the following:

I. REAL PARTY IN INTEREST

The real party in interest is NIHON MEDI-PHYSICS CO., LTD. of Japan.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1 to 29 are all of the claims that have been presented in this application.

Claims 1 to 13, 20, 28 and 29 have been canceled.

The claims on appeal are claims 14 to 19 and 21 to 27.

IV. STATUS OF AMENDMENTS

An Amendment Under 37 C.F.R. § 1.116 was filed on May 24, 2004. In an Advisory Action of June 21, 2004, the Examiner indicated that this Amendment would be entered.

V. SUMMARY OF THE INVENTION

The present invention, as set forth in claim 14, is directed to a method for the *in vivo* administering of a drug with binding affinity for plasma protein, wherein, in the administration of a first drug with binding affinity for plasma protein, a second drug, which is verapamil (page 6, line 9 and page 12, line 14), with binding affinity for the same plasma protein for which the first drug has binding affinity, is administered simultaneously with the first drug or before or after the administration of the first drug to thereby regulate the binding of the first drug to the plasma protein. (Page 3, line 21 to page 4, line 3; page 11, lines 4 to 7; page 16, line 4).

In another aspect, as set forth in claim 21, the present invention is directed to a pharmaceutical preparation for regulating binding affinity of a first drug for plasma protein, which comprises a first drug with binding affinity for plasma protein and a single or plural second drug with binding affinity for the same plasma protein, for which the first drug has binding affinity. (Page 4, lines 17 to 20).

VI. ISSUES

1) Whether the Examiner was correct in rejecting claims 14 and 15 under 35 U.S.C. § 102(b) as anticipated by Pritchard et al. (Claim 20 which had also been subject to this rejection has been canceled).

2) Whether the Examiner was correct in rejecting claims 14 to 17, 21, 23 and 25 under 35 U.S.C. § 102(b) as anticipated by Somogyi et al. (Claims 20, 28 and 29 which had been subject to this rejection have been canceled).

3) Whether the Examiner was correct in rejecting claims 14 and 16 to 19 and 21 to 27 under 35 U.S.C. § 103(a) as obvious over Somogyi et al in view of Li et al. (Claims 20, 28 and 29 which had been subject to this rejection have been canceled).

VII. GROUPING OF CLAIMS

For purposes of this appeal, the claims stand or fall together.

VIII. ARGUMENTS

A. The Rejection of Claims 14 and 15 under 35 U.S.C. § 102(b) as Anticipated by Pritchard et al.

Appellants submit that Pritchard et al do not disclose or render obvious the presently claimed invention and, accordingly, request reversal of this rejection.

The present invention, as set forth in claim 14, is directed to a method of administering *in vivo* a drug with binding affinity for plasma protein, wherein, in the administration of a first drug

with binding affinity for plasma protein, a second drug, which is verapamil, with binding affinity for the same plasma protein for which the first drug has binding affinity, is administered simultaneously with the first drug or before or after the administration of the first drug to thereby regulate the binding of the first drug to the plasma protein.

Pritchard et al disclose *in vitro* tests to investigate the plasma protein binding of bepridil using radiolabeled bepridil (bepridil-14C). Pritchard et al nowhere disclose an *in vivo* administering of a second drug (such as verapamil) to regulate the binding of a first drug to plasma protein.

Pritchard et al disclose, at page 348, column 2, "Effects of Other Drugs", the general procedure they employed to determine the effects of other drugs on the *in vitro* plasma protein binding of bepridil.

Pritchard et al disclose the results of the *in vitro* tests at page 351, left hand column, first complete paragraph, and in Table V at page 351. In particular, Pritchard et al disclose that the addition of verapamil, diltiazem and disopyramide at ten- to 100-fold molar excess over bepridil resulted in significant displacement of bepridil from its plasma protein binding sites, but that there were no changes in bepridil plasma binding when the drugs were present at equimolar concentrations or less.

On page 352, right hand column, Pritchard et al state that verapamil appears to displace bepridil if added in a ten or 100-fold molar excess, and that such a concentration is many times greater than that achieved clinically.

The abstract of Pritchard et al discloses that free fractions of bepridil were enhanced by addition of drugs such as (verapamil, nifedipine, diltiazem, disopyramide and warfarin), but only at concentration above those achieved clinically.

Accordingly, appellants submit that Pritchard et al do not disclose or suggest that verapamil can be administered *in vivo* as a second drug to regulate the binding of bepridil. Pritchard et al only disclose an *in vitro*, not an *in vivo* administering. Further, Pritchard et al disclose that the amount of verapamil necessary to affect the binding is greater than the amounts that are clinically employed and, therefore, teach against a method of the *in vivo* administering of drugs in accordance with the method set forth in the present method claims 14 and 15.

In sum, Pritchard et al do not disclose or suggest that verapamil can be administered *in vivo* as a second drug to regulate the binding of bepridil, since Pritchard et al disclose an *in vitro* test, and state that the *in vitro* amount of verapamil in Pritchard et al necessary to affect the binding is greater than the amounts that are clinically employed.

In view of the above, appellants submit that Pritchard et al do not disclose or render obvious the presently claimed invention and, accordingly, request reversal of this rejection.

B. The Rejection of Claims 14 to 17, 21, 23 and 25 under 35 U.S.C. § 102(b) as anticipated by Somogyi et al.

Appellants submit that Somogyi et al do not disclose or render obvious the presently claimed invention and, accordingly, request reversal of this rejection.

Somogyi et al discuss the pharmokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis.

Somogyi et al discuss the binding to plasma protein at a number places, but as discussed in detail below, none of the various disclosures of plasma protein binding in Somogyi et al teaches or suggests the administering of a second drug that regulates the binding of the first drug to the plasma protein. Somogyi et al disclose that the plasma protein binding remained unchanged, and thus teach away from the regulation of the binding.

At page 52 of Somogyi et al, in the section entitled "Plasma protein binding and erythrocyte distribution", Somogyi et al discuss plasma protein binding, but Somogyi et al nowhere disclose or suggest the administering of a second drug that regulates the binding of the first drug to the plasma protein.

The Somogyi et al discussion at page 52, which continues on to page 53, merely discusses how the protein binding of verapamil was determined, and does not set forth any of the results of the determination. Thus, the discussion at pages 52 and 53 does not indicate that a second drug regulated the plasma protein binding of the first drug.

Moreover, the procedure set forth at pages 52 and 53 would not be able to determine whether a second drug regulated the plasma protein binding of the first drug because the procedure does not measure the plasma protein binding with a first drug and compare it to the plasma protein binding obtained with a first and second drug. The procedure merely measures the plasma protein binding at different concentrations of a single drug.

The places where Somogyi et al do disclose the results of that determination are as follows:

(i) In the abstract, in item 4, Somogyi et al state that "Plasma protein binding remained unchanged." As discussed in subsections (ii), (iii) and (iv) below, appellants submit that this indicates that the plasma protein binding was unchanged between healthy patients and liver cirrhotic patients and, therefore, teaches away from the regulation of the binding.

(ii) At page 54, right hand column, last word, to page 55, left hand column, Somogyi et al contain the following discussion:

> In the liver cirrhotic patients, the free fraction of verapamil in plasma was on average 8.0 (range 7.3 to 8.9)% and was independent of the total verapamil concentration ($P>0.05$). This free fraction was not different to those reported by us (range 7.8 to 11.3%) previously (Schomerus *et al.*, 1976).

This discussion indicates that the plasma protein binding was unchanged between healthy patients and liver cirrhotic patients, and does not contain any information concerning regulation of the plasma protein binding by use of a second drug. To the extent it contains any information

concerning the regulation of plasma protein binding by use of a second drug, it shows that there was no regulation.

Thus, this section of Somogyi et al indicates that plasma protein binding was unchanged between healthy patients and liver cirrhotic patients, and does not contain any information concerning regulation of the plasma protein binding by use of a second drug.

(iii) Somogyi et al, at page 55, left hand column, first complete paragraph, contain the following statement:

> The increased volume of distribution and unaltered plasma protein binding of verapamil resulted in an approximately 25% decrease, from 0.73 to 0.5% in the free fraction bound to tissues (see **Methods**).

This discussion in Somogyi et al confirms that Somogyi et al teach that plasma protein binding was unchanged, that is, there was an "unaltered plasma protein binding".

Again, this discussion means that the plasma protein binding was unchanged between healthy patients and liver cirrhotic patients.

(iv) Somogyi et al, at page 58, left hand column, under the heading "Discussion" state as follows:

> Since protein binding remained unchanged an approximately 25% decrease in the free fraction bound to tissue is calculated which together with the 28% increase in total body water (Schober *et al.*, 1979) is proposed to explain the increased volume of distribution.

Again, appellants submit that this disclosure in Somogyi et al indicates that there was no change in the plasma protein binding between healthy patients and liver cirrhotic patients, and does not contain any information concerning regulation of the plasma protein binding by a second drug.

In summary, the various portions of Somogyi et al that discuss plasma protein binding do not teach or suggest the regulation of the plasma protein binding by use of verapamil as a second drug.

In addition to the discussion in Somogyi et al of protein binding, the Examiner appears to be relying on other disclosures of Somogyi et al, each of which, according to the Examiner, satisfies the recitations of the present claims.

First, the Examiner has asserted that Somogyi et al disclose that both an intravenous dose and an oral dose of verapamil are administered simultaneously. See page 51, "Introduction", right-hand column, where Somogyi et al disclose that the aim of their study was to investigate the influence of liver cirrhosis on the pharmokinetics and bioavailability of verapamil using a stable labeled oral solution of verapamil and simultaneous administration of an unlabelled intravenous dose of the drug. The Examiner has asserted that the present claims do not require that the two drugs be different, and that the disclosure in Somogyi et al of two different dosage forms of the same drug satisfies the recitations of the present claims.

The Examiner has specifically referred to page 52 to columns 1 and 2, the bridging paragraph, as disclosing that verapamil was administered by intravenous and oral route simultaneously using stable labeled techniques and that the intravenous (unlabeled) dose was given at a constant infusion of 10 mg verapamil dissolved in 10 ml physiologically saline over five minutes and the oral dose of 40 mg HCl consisted of d_3-verapamil given in solution form 30 minutes after the end of the intravenous infusion. The Examiner has also pointed out that Somogyi et al disclose that the controlled subjects received the same intravenous doses, but 80 mg d_3-verapamil orally.

Appellants do not dispute that Somogyi et al disclose the simultaneous administration of verapamil by both intravenous and oral route. Appellants do not see how this point is relevant to the rejection.

Appellants maintain that Somogyi et al nowhere disclose the administering of verapamil as a second drug that regulates the binding of a first drug to the plasma protein. The results of the simultaneous administration of verapamil by both intravenous and oral route are reported by Somogyi et al in the portions discussed in items (i) to (iv) above. As can be seen from that discussion, Somogyi et al do not disclose or suggest the regulation of the binding by administering a second drug.

The Examiner also has relied on the fact that Somogyi et al disclose that antipyrine and indocyanine green were administered as a bolus dose to a patient that was being treated with verapamil.

Somogyi et al disclose, at page 54, that in all seven patients that were tested, the antipyrine saliva clearance was reduced from normal values and that the indocyanine green blood clearance was reduced.

Again, appellants do not see any discussion of regulation of protein binding in this disclosure. Clearance is not necessarily related to protein binding.

The Examiner has also relied on the disclosure at page 59 of Somogyi et al that most of the patients being treated with verapamil were receiving cimetidine and/or spironolactone, and the statement in Somogyi et al at page 59 that the co-administration of these drugs with verapamil may have affected the bioavailability and oral clearance of verapamil.

This disclosure does not state that bioavailability and clearance were, in fact, affected, but only speculates that they may have been affected. Further, even if bioavailability and clearance were affected, this does not indicate that plasma protein binding was involved. Appellants do not see any discussion or disclosure of the regulation of protein binding in this discussion.

In view of the above, appellants submit that Somogyi et al do not defeat the patentability of the present claims and, accordingly, request reversal of this rejection.

C. The Rejection of Claims 14 and 16 to 19 and 21 to 27 under 35 U.S.C. § 103(a) as Obvious over Somogyi et al in view of Li et al.

Appellants submit that these references do not disclose or render obvious the presently claimed invention and, accordingly, request reversal of this rejection.

Appellants have discussed Somogyi et al in detail above, and rely on that discussion.

Thus, as discussed above, Somogyi et al do not disclose or suggest the *in vivo* administering of a second drug (verapamil) that regulates the binding of the first drug to the plasma protein.

The Examiner, during prosecution, had relied on the Li et al patent for a teaching of water-soluble polymer conjugate of "other therapeutic drugs" which include verapamil, and for a teaching of water-soluble pro-drugs. The Examiner stated that the complexes in Li et al may be radiolabeled with various metals or conjugated to various chelators, and that the complexes may be imaged using single photo emission computer topography or positron emission tomograpy. The Examiner stated that Li et al disclose that verapamil can be used in combination with another drug that may be radiolabeled.

The Examiner asserted that it would have been obvious to modify the invention of Somogyi et al et al by using the teachings of Li et al, and generate a kit comprising first and second drugs and attach various radiolabels and/or a chelators, because Li et al disclose a composition wherein verapamil may be added to generate a water soluble polymer conjugate.

Although the Examiner has stated that Li et al disclose that verapamil can be used in combination with another drug that may be radiolabeled, appellants have not found any such disclosure in Li et al. Li et al merely disclose that verapamil can be used to make a water soluble polymer conjugate, and that water soluble metal chelator conjugates of Li et al can contain a radionuclide in certain embodiments. Li et al disclose that the water soluble conjugates can be administered in conjunction with other drugs, but do not disclose that these other drugs may be radiolabeled.

Further, Li et al do not supply the deficiencies of Somogyi et al that have been discussed above. Thus, Li et al do not disclose or suggest the *in vivo* administering of a second drug that regulates the binding of the first drug to plasma protein.

Since there is no disclosure or suggestion in Somogyi et al or Li et al with regard to the regulation of the plasma protein binding of a first drug by administering a second drug, appellants submit that one of ordinary skill in the art could not arrive at the present invention from the combined teachings of Somoygi et al and Li et al.

In view of the above, appellants submit that the cited references do not defeat the patentability of the presently claimed invention and, accordingly, request reversal of this rejection.

The present Brief on Appeal is being filed in triplicate. Unless a check is submitted herewith for the fee required under 37 C.F.R. §1.192(a) and 1.17(c), please charge said fee to Deposit Account No. 19-4880.

Respectfully submitted,

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Date: August 24, 2004

APPENDIX

CLAIMS 14 to 19 and 21 to 27 ON APPEAL:

Claim 14. Method of in-vivo administration of drugs with binding affinity for plasma protein, which is characterized in that, in the administration of a first drug with binding affinity for plasma protein, verapamil as a second drug with binding affinity for the same plasma protein for which the first drug has binding affinity, is administered simultaneously with the first drug or before or after the administration of the first drug to thereby regulate the binding of the first drug to the plasma protein.

Claim 15. The method of the administration of drugs with binding affinity for plasma protein according to Claim 14, wherein the second drug has binding affinity to the same binding sites on plasma protein to which the first drug has binding affinity.

Claim 16. The method of the administration of drug with binding affinity for plasma protein according to Claim 14, wherein the first drug is a radiodiagnostic drug for in vivo use or a radiotherapeutic drug for in vivo use.

Claim 17. The method of the administration of drugs with binding affinity for plasma protein according to Claim 15, wherein the first drug is a radiodiagnostic drug for in vivo use or a radiotherapeutic drug for in vivo use.

Claim 18. The method of the administration of drugs with binding affinity for plasma protein according to Claim 16 or 17, wherein the radiodiagnostic drug for in vivo use or the

radiotherapeutic drug for in vivo use is radiolabeled with one nuclide selected from the group consisting of 11-carbon (^{11}C), 15-oxygen (^{15}O), 18-fluorine (^{18}F), 32-phosphorus (^{32}P), 59-iron (^{59}Fe), 67-copper (^{67}Cu) , 67-gallium (^{67}Ga), 81m-krypton (^{81m}Kr), 81-rubidium (^{81}Rb), 89-strontium (^{89}Sr), 90-yttrium (^{90}Y), 99m-technetium (^{99m}Tc), 111-indium (^{111}In), 123-iodine (^{123}I), 125-iodine (^{125}I), 131-iodine (^{131}I), 133-xenon (^{133}Xe), 117m-tin (^{117m}Sn), 153-samarium (^{153}Sm), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 201-thallium ($^{201}T1$), 212-bismuth (^{212}Bi), 213--bismuth (^{213}Bi) and 211-astatine (^{211}At).

Claim 19. The method of the administration of drugs with binding affinity for plasma protein according to Claim 16 or 17, wherein the first drug has one group labeled with nuclide and the group is selected from the group consisting of a bisaminothiol compound, a monaminomonoamidobisthiol compound, a bisamidobisthiol compound, a mercaptoacetylglycylglycylglycine compound, a hexamethylpropyleneamineoxime compound, an ethylenebis [bis(2-ethoxyethyl) phosphine] compound, a 2,3-dimercaptosuccinic acid compound, an ethylenecysteine dimer compound, a methoxyisobutylisonitrile compound, a polyamine compound, a pyriodoxylydeneaminate compound, methylene diphosphonate, a hydroxymethylene diphosphonate compound, a ß-methyl-ω-phenylpentadecanoic acid compound, N-isopropylamphetamine, hippuric acid, benzylguanidine and a tropane compound.

Claim 21. A pharmaceutical preparation for regulating binding affinity of a first drug for plasma protein, which comprises a first drug with binding affinity for plasma protein and

verapamil as a second drug with binding affinity for the same plasma protein, for which the first drug has binding affinity.

Claim 22. The pharmaceutical preparation according to Claim 21, wherein each of the first drug and the second drug is in a separate container, and prepared as a kit.

Claim 23. The pharmaceutical preparation according to Claim 21, wherein the second drug has binding affinity to the same binding sites on the plasma protein, to which the first drug has binding affinity.

Claim 24. The pharmaceutical preparation according to Claim 22, wherein the second drug has binding affinity to the same binding sites on the plasma protein, to which the first drug has binding affinity.

Claim 25. The pharmaceutical preparation according to any one of Claims 21 to 24, wherein the first drug is a radiodiagnostic drug for in vivo use or a radiotherapeutic drug for in vivo use.

Claim 26. The pharmaceutical preparation according to Claim 25, wherein the radiodiagnostic drug for in vivo use or the radiotherapeutic drug for in vivo use is radiolabeled with one nuclide selected from the group consisting of 11-carbon (^{11}C), 15-oxygen (^{15}O), 18-fluorine (^{18}F), 32-phosphorus (^{32}P), 59-iron (^{59}Fe), 67-copper (^{67}Cu), 67-gallium (^{67}Ga), 81m-krypton (^{81m}Kr), 81-rubidium (^{81}Rb), 89-strontium (^{89}Sr), 90-yttrium (^{90}Y), 99m-technetium (^{99m}Tc), 111-indium (^{111}In), 123-iodine (^{123}I), 125-iodine (^{125}I), 131-iodine

(^{131}I), 133-xenon (^{133}Xe), 117m-tin (^{117m}Sn), 153-samarium (^{153}Sm), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 201-thallium (^{201}Tl), 212-bismuth (^{212}Bi), 213-bismuth (^{213}Bi) and 211-astatine (^{211}At).

Claim 27. The pharmaceutical preparation according to Claim 25, wherein the first drug has one group labeled with nuclide and the group is selected from the group consisting of a bisaminothiol compound, a monaminomonoamidobisthiol compound, a bisamidobisthiol compound, a mercaptoacetylglycylglycylglycine compound, a hexamethylpropyleneamineoxime compound, an ethylenebis [bis(2-ethoxyethyl) phosphine] compound, a 2,3-dimercaptosuccinic acid compound, an ethylenecysteine dimer compound, a methoxyisobutylisonitrile compound, a polyamine compound, a pyriodoxylydeneaminate compound, methylene diphosphonate, a hydroxymethylene diphosphonate compound, a ß-methyl-ω-phenylpentadecanoic acid compound, N-isopropylamphetamine, hippuric acid, benzylguanidine and a tropane compound.

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SUBMISSION OF APPELLANT'S BRIEF ON APPEAL

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Sir:

Submitted herewith please find an original and two copies of Appellant's Brief on Appeal. A check for the statutory fee of $330.00 is attached. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this paper is attached.

Respectfully submitted,

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